

REMARKS

In this communication, Claims 84, 104, 122, and 145 have been amended. Claims 84-147 are pending. The Examiner's rejections are as follows:

- I) Claims 84-89, 91-92, 95-97, 100-110, 113-115, 118-127, 133-138, and 140-147 were rejected under 35 U.S.C. 103(a) as allegedly obvious over Kurn et al. (U.S. Pat. 6,251,639) in view of Shibata et al. (Genome Res., 5:400-403; 1995); and
- II) Claims 90, 93-94, 98-99, 111-112, 116-117, 128-132, and 139 were rejected under 35 U.S.C. 103(a) as allegedly obvious over Kurn et al. in view of Dean et al. (U.S. Pat. 6,977,148).

I. Obviousness Rejection over Kurn et al. in view of Shibata et al.

The Examiner rejected Claims 84-89, 91-92, 95-97, 100-110, 113-115, 118-127, 133-138, and 140-147 under 35 U.S.C. 103(a) as allegedly obvious over Kurn et al. (U.S. Pat. 6,251,639) in view of Shibata et al. (Genome Res., 5:400-403; 1995) (Office Action, page 3). Applicants disagree with this rejection and submit that the Examiner has failed to establish a *prima facie* case of obviousness. For example, the Examiner has failed to establish a reasonable expectation of successfully combining the Kurn et al. and Shibata et al. references.

A. Kurn et al. Clearly Indicates That There is No Reasonable Expectation of Successfully Combining the References

The Examiner cites Kurn et al. as allegedly teaching all the elements of the claims except for the use of primers composed only of ribonucleotides (Office Action, page 5). The Examiner attempts to make up for the lack of teaching in Kurn et al. by citing the Shibata et al. reference as teaching primers composed of only ribonucleotides (Office Action, page 5). The Kurn et al. reference, however, clearly indicates that the use of *composite* primers, composed of both RNA and DNA, are critical to the success of the disclosed methods. Applicants submit that the Examiner has improperly ignored the full teaching of the Kurn et al. reference.

Under the law, the Examiner cannot simply select isolated portions of a prior art reference, but instead, the prior art reference must be considered in its *entirety*. MPEP 2141.02.

As stated by the Federal Circuit:

"It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Hedges*, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986).

In this case, the Examiner has failed to consider the great importance Kurn et al. placed on the use of composite primers. For example, Kurn et al. describes the importance of using composite primers in the disclosed methods:

The composite design of the primer is critical for subsequent displacement of the primer extension product by binding of a new (additional) composite primer and the extension of the new primer by the polymerase. (*emphasis added*, Col. 17, lines 10-13).

Not only does Kurn et al. emphasize the critical nature of using composite primers, but the entire description, and all of the figures, in this lengthy reference only describe the use of composite primers (i.e., there is not even a prophetic sentence or two on using all RNA primers). For example, the Kurn et al. reference states:

"The amplification methods of the invention employ a single composite primer that is composed of RNA and DNA portions." (col. 17, lines 8-10).

As such, Applicants respectfully submit that the Examiner has improperly ignored the full teaching of the Kurn et al. reference, particularly the importance of composite primers in the disclosed methods, and instead, has simply chosen so much of this reference that would support the current obviousness rejection, to the exclusion of the full teaching of the reference.

In light of the full teaching in Kurn et al., it is clear that the combination of Kurn et al. and Shibata et al. would not lead to a reasonable expectation of successfully yielding the claimed invention. For example, since Kurn et al. teaches that use of composite primers is critical to the success of the amplification methods, one skilled in the art would have no basis to expect that such methods could be successfully conducted by using primers composed entirely of RNA. Indeed, the Kurn et al. reference serves as an important "teach-away," that would lead one of skill in the art away from the present invention. As such, Applicants submit that no *prima facie* case of obviousness has been established and therefore, this rejection should be withdrawn.

B. Examiner's Motivation to Combine Rests on Hindsight Reconstruction

Applicants note that the motivation to combine the Kurn et al. and Shibata et al. references cited by the Examiner rests of an alleged reasonable expectation of successfully combining the references (Office Action, page 5). As explained above, there is no reasonable expectation of successfully combining Kurn et al. and Shibata et al. in light of the composite primer teachings in the Kurn et al. reference. Since there is no reasonable expectation of successfully combining the references, the Examiner's motivation for combining these references also fails. This is a second reason that no *prima facie* case of obviousness has been established by the Examiner.

Applicants note that given the lack of motivation to combine the references, the only apparent basis for combining the references is based on impermissible hindsight reconstruction (i.e., the Examiner's using the success of the amplification method in the present application as a guide in an attempt to piece together the claimed invention from the prior art). Such hindsight reconstruction, under the law, is not permissible. As such, Applicants submit that this obviousness rejection should be withdrawn.

C. Amendment to the Claims

As described above, it is clear that there is no reasonable expectation to successfully combine the Kurn et al. reference with the Shibata et al. reference. Nonetheless, to expedite the prosecution of the present application, without acquiescing to the Examiner's rejection, while reserving the right to prosecute the original claims in the future, Applicants have amended the claims. In particular, Claims 84, 104, and 122 have been amended to recite that the DNA polymerase "lacks 5' to 3' exonuclease activity." Support for this amendment can be found in the specification at, for example, paragraph 117.

This amendment further highlights the patentability of the claims. For example, the Shibata et al. reference, in describing the use of RNA primers, teaches that:

[u]se of rTth DNA polymerase is essential because it has strong reverse transcriptase activity. (*emphasis added*, Abstract).

The Tth DNA polymerase is a DNA polymerase which has, in addition to reverse transcriptase activity (in the presence of manganese cations), 5' to 3' exonuclease activity. As Shibata et al.

recite the use of a polymerase that has 5' to 3' exonuclease activity, and the claims have been amended to recite the use of DNA polymerases without such activity, this is an additional reason that this obviousness rejection should be withdrawn.

Applicants further note that Shibata et al. states that DNA primers are more efficient than RNA primers for PCR (page 401, right col., last para.), so there was no reason or benefit (other than price) for using such RNA primers for PCR. Thus, scientifically speaking, the choice of an RNA primer rather than a DNA primer for PCR was arbitrary at best and disadvantageous at worst.

II. Obviousness Rejection over Kurn et al. in view of Dean et al.

The Examiner rejected Claims 90, 93-94, 98-99, 111-112, 116-117, 128-132, and 139 under 35 U.S.C. 103(a) as allegedly obvious over Kurn et al. in view of Dean et al. (U.S. Pat. 6,977,148) (Office Action, page 6). Applicants disagree with this rejection and submit that the Examiner has not properly characterized the Dean et al. reference and has failed to establish a *prima facie* case of obviousness. For example, the Examiner has failed to establish a reasonable expectation of successfully combining the Kurn et al. and Dean et al. references.

A. The Examiner has not properly characterized the Dean et al. reference

The Examiner cites Kurn et al. as allegedly teaching all the elements of the claims except for the use of primers composed only of ribonucleotides and modified ribonucleotides (Office Action, page 6). The Examiner attempts to make up for the lack of teaching in Kurn et al. by citing the Dean et al. reference as teaching primers composed of only ribonucleotides and modified ribonucleotides (Office Action, page 6). However, rather than simply citing Dean et al. for such riboprimers, the Examiner further characterizes the methods of Dean et al. as allegedly embodying the entire claimed invention, citing three steps of: (a) hybridizing, (b) extending, and (c) cleaving the annealed riboprimers (Office Action, page 6).

Applicants respectfully submit that the Examiner has not properly characterized the Dean et al. reference. For example, the Examiner alleges that Dean teaches the following step (c)

(c) cleaving the annealed riboprimers to the template and repeats primer extension, whereby multiple copies of the complementary sequence of the target nucleic acid are produced (citing col. 34, lines 36-67, and col. 36, lines 10-51).

It is unclear what "cleaving the annealed riboprimer to the template" means, but it would appear that the Examiner is suggesting that once a riboprimer is employed, it is digested (e.g., digested with RNase H given the column 34 passage cited). Applicants note that neither of the passages cited by the Examiner (nor any other part of Dean et al.) teaches digesting the riboprimer with RNase H as recited in the present claims. The only passage in Dean et al. that even mentions RNase H is at column 34, lines 35-51. In this passage, Dean et al. describe using RNase H to digest a *target RNA template* after cDNA has been made using a reverse transcriptase. The resulting single stranded cDNA is then used in multiple displacement amplification. Nowhere in this discussion (or in the rest of the reference) does Dean et al. describe the use of RNase H to cleave an annealed riboprimer with RNase H such that another primer can hybridize to the same template to repeat primer extension. As such, it is clear that the Dean et al. reference does not teach the method step of the claimed invention as apparently alleged by the Examiner.

B. Kurn et al. Clearly Indicates That There is No Reasonable Expectation of Successfully Combining the References

In light of the above discussion, the relevant part of the Dean et al. reference is the discussion of riboprimers composed of RNA and modified RNA. However, the combination of this teaching from Dean et al. and the Kurn et al. reference would not lead to a reasonable expectation of successfully producing the claimed invention. As outlined in detail above, the Kurn et al. reference clearly indicates that the use of *composite* primers, composed of both RNA and DNA, are critical to the success of the disclosed methods. In light of the full teaching in Kurn et al. (which must be considered by the Examiner) it is clear that the combination of Kurn et al. and Dean et al. would not lead to a reasonable expectation of successfully yielding the claimed invention. For example, since Kurn et al. teaches that use of composite primers is critical to the success of the amplification methods, one skilled in the art would have no basis to expect that such methods could be successfully conducted by using primers composed entirely of RNA and modified RNA. Indeed, the Kurn et al. reference serves as an important "teach-away," that would lead one of skill in the art away from the present invention. As such, Applicants submit that no *prima facie* case of obviousness has been established and therefore, this rejection should be withdrawn.

CONCLUSION

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned at 608-218-6900.

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/ Jason R. Bond /
Jason R. Bond
Registration No. 45,439
CASIMIR JONES S.C.
440 Science Drive, Suite 203
Madison WI 53711
608.218.6900